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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,333	03/25/2004	Alan J. Heeger	UCSB-510CIP	8242

24353 7590 08/15/2007

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EXAMINER
CROW, ROBERT THOMAS

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,333	HEEGER ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8,12-16,25-34,39,40,47,48,55,56 and 59-62* is/are pending in the application.

4a) Of the above claim(s) *39,40,47,48,55,56 and 59-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,12-16 and 25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. This action is in response to after-final papers filed 4 June 2007 in which claims 1, 16, 25, 34, 39-40, 47-48, 55, and 59 were amended, claims 51-54 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) are withdrawn in view of the amendments.

Applicant's arguments filed 4 June 2007 (i.e., the "Remarks") regarding the teachings of Lee et al have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Blackburn et al as described below.

In view of Applicant's request on page 11 of the Remarks that the request for a terminal disclaimer be held in abeyance, the previous rejections under the judicially created doctrine of obviousness-type double patenting over claims 1-14 of copending Application No. 11/193,318 are maintained for the reasons set forth in the previous Office Action.

Applicant further requests on page 11 of the Remarks that the request for a terminal disclaimer against Application 10/678,760 be held in abeyance. However, as noted in the previous Office Action, the rejections have been **withdrawn** in view of Applicant's abandonment of the conflicting application.

Claims 1, 7-8, 12-16, 25, and 28-34 are under prosecution.

Request for Corrected Filing Receipt and Application Data Sheet

2. The Request for Corrected Filing Receipt and Application Data Sheet filed 19 June 2007 are acknowledged. The domestic priority data has been changed to read "This appln is a CIP of 10/678,760 10/03/2003 which claims benefit of 60/457,762 03/25/2003".

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7-8, 12-16, 25, and 28-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claims 1 and 25 are drawn to a second position (i.e., distance) that "provides more efficient electron transfer between the redox moiety and the electrode[;]"e.g., the last 3 lines of each of claims 1 and 25. A review of the specification yields not teaching of "more efficient" electron transfer. Applicant cites paragraphs 0046, 0052, and 0055 as support for this limitation. While paragraph 0055 implies that moving the electrode closer to the electrode results in a "signal-on" process, none of the cited paragraphs teach "more efficient" electron transfer.

Applicant further cites Figures 2-4 as support for the amendment. It is noted that while Figure 2 does not show the target 28 bound to the probe, Figure 2 does show label 24 closer to the electrode in the second position. It is also noted that Figure 3 does not necessarily form the structure shown on the right of the Figure 3, but, depending on the polarity of the target strand, can also form a structure wherein the single stranded region between 35 and 37 on target 38 would be the right half of a "bubble," wherein the left half of the "bubble" would be the single stranded region between 31 and 33 on the probe. Thus, Figure 3 does not demonstrate this arrangement of the strands, and it is thus unclear if the alternate structure presented by the examiner would place the label in a "more efficient" position. Figure 4 shows label 44 on target 42, rather than probe 40, as required by the instant claims, and does not support the instant claims.

Thus, the specification does not teach what is encompassed by the term "more efficient" electron transfer and the amendments introduce new matter.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-13 are each indefinite in the recitation "the second configuration" in line 1 of each of claims 12-13. The recitation "the second configuration" lacks antecedent basis in the second "position" of claim 1. It is suggested the phrase "configuration" be changed to "position."

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 7-8, 12, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn et al (U.S. Patent No. 6,264,825 B1, issued 24 July 2001) in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994).

Regarding claims 1 and 12, Blackburn et al teach a detector. In a single exemplary embodiment, Blackburn et al teach a detector comprising an electrode capable of sensing redox events in a redox moiety in the form of a detection electrode for detecting electron transfer (column 2, lines 14-24). A probe is immobilized on the detection electrode (column 13, lines 10-13). The probe of Blackburn et al comprises a redox moiety in the form of an ETM (column 66, lines 9-44) wherein an ETM is an electron transfer moiety (i.e., redox moiety; Abstract).

Blackburn et al further teach the probe is an oligonucleotide having a hairpin stem-loop structure with the redox moieties 135 at an end of the probe (column 66, lines 9-44 and Figure 12), wherein either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25). Thus, Blackburn et al teach an embodiment wherein in the absence of the specific interaction of hybridization between the target at the probe, redox moiety 135 is in a first position. Upon binding to the target, the hairpin stem loop structure is altered, which moves the redox moiety to a second position. The first and second positions give rise to distinguishable redox events detectable by the electrode because detection of the binding proceeds through the use of the ETM redox moieties (Abstract).

Blackburn et al also teach either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25). Therefore, one terminus of the probe is immobilized and the redox moiety 135 at the other terminus.

Blackburn et al do not teach the end of the probe bearing the redox moiety moves closer to the electrode upon binding the target; i.e., wherein the second position is closer to the electrode than the first position, thereby providing more efficient electron transfer to the electrode (i.e., claim 1), or wherein the second configuration comprises internal hybridization between two regions of the probe (i.e., claim 12).

However, Lizardi et al teach a single switch probe nucleic acid molecule having two alternate conformations in the presence and absence of a target molecule 8 (column 14, Example V and Figures 12-15). Figure 12 illustrates the probe 30 in the absence of an oligonucleotide target, and Figure 13 shows the alternate conformation of the probe in the presence of the target 8 (column 14, Example V). Figure 13 further shows internal hybridization between two regions of the probe because hairpin 36 is formed after binding to the target (i.e., claim 12). Lizardi et al also teaches the probes have the added advantage of allowing exponential replication of the target polynucleotide (column 14, lines 40-41), which generates up to a billion copies of a single target molecule in a single step (column 3, lines 48-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the detector comprising a probe having one terminus immobilized and the other terminus labeled with a redox moiety as taught by Blackburn et al with the switch probe of Lizardi et al with a reasonable expectation of success. The modification would result in the probe of Lizardi et al being immobilized at end 35 as shown if Figure 12 of Lizardi et al and the redox moiety at end 32 in accordance with the immobilization and labeling taught by Blackburn et al. Upon binding, end 32 would move closer to end 35, as depicted in Figure 13, thereby making the second position provide more efficient electron transfer to the electrode because the redox moiety is now closer to the electrode. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a detector having the added advantage of having probes that allow production of a billion copies of a potentially scarce target in a single step amplification of as explicitly taught by Lizardi et al (column 3, lines 48-50).

Regarding claim 7, the detector of claim 1 is discussed above. Blackburn et al further teach the probe is immobilized on the electrode on a position distant from the redox moiety because either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25) and the redox moiety 135 at the other terminus (Figure 12)

Regarding claim 8, the detector of claim 1 is discussed above. Blackburn et al further teach the electrode is capable of inducing redox events in the redox moiety; namely, the detector comprises an amperometric device for applying a potential to the electrode and different currents result because of electron transfer (column 82, lines 7-20).

Regarding claims 14-15, the detector of claim 1 is discussed above. Blackburn et al further teach the electrode comprises a metal; namely, gold (column 2, lines 60-65).

Regarding claim 16, the detector of claim 1 is discussed above. Blackburn et al further teach the redox moiety is ethidium bromide (column 49, lines 15-40).

Regarding claim 25, Blackburn et al teach a detector. In a single exemplary embodiment, Blackburn et al teach a detector comprising an electrode capable of sensing redox events in a redox moiety in the form of a detection electrode for detecting electron transfer (column 2, lines 14-24). A probe is immobilized on the detection electrode (column 13, lines 10-13). The probe of Blackburn et al comprises a redox moiety in the form of an ETM (column 66, lines 9-44) wherein an ETM is an electron transfer moiety (i.e., redox moiety; Abstract).

Blackburn et al further teach the probe is an oligonucleotide having a hairpin stem-loop structure with the redox moieties 135 at an end of the probe (column 66, lines 9-44 and Figure 12), wherein either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25). Thus, Blackburn et al teach an embodiment wherein in the absence of the specific interaction of hybridization between the target at the probe, redox moiety 135 is in a first position. Upon binding to the target, the hairpin stem loop structure is altered, which moves the redox moiety to a second position. The first and second positions give rise to distinguishable redox events detectable by the electrode because detection of the binding proceeds through the use of the ETM redox moieties (Abstract).

Blackburn et al also teach either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25). Therefore, one terminus of

the probe is the instantly claimed first region that is immobilized to the electrode and the redox moiety 135 at the other terminus, which is the instantly claimed third region. The intermediate nucleotides are the second region, which form a first loop by hybridization of first and second nucleotide sequences within the second region (e.g., Figure 12).

Blackburn et al do not teach the end of the probe bearing the redox moiety moves closer to the electrode upon binding the target; i.e., wherein the second position is closer to the electrode than the first position, thereby providing more efficient electron transfer to the electrode, or wherein the second region forms a second hybridization loop upon binding the target between two regions of the probe.

However, Lizardi et al teach a probe nucleic acid that is a single molecule (e.g., column 14, Example V and Figures 12-13). Figure 12 illustrates the probe 30 in the absence of an oligonucleotide target, and Figure 13 shows the alternate conformation of the probe in the presence of the target (column 14, Example V). Lizardi et al teach the probe has switch sequences, which hybridize to each other in the absence of a target (column 5, lines 45-50). Figure 12 comprises element 32, wherein the terminus at 32 is the third region. Lizardi et al also teach switch sequences and probe sequences overlap (column 7, lines 47-55); thus, the second region of the instantly claimed probe comprises the remainder of element 32 as well as elements 33 and 34. The second region self hybridizes to form first loop 31 and a stem between part of 32 and 33, which are the first and second nucleotide sequences. The third region of the probe is element 35, which is located at the other end of the probe.

Figure 13 shows that upon hybridization to oligonucleotide target 8, loop 31, which is the probe sequence, is hybridized to the target. Because Lizardi et al teach switch sequences and probe sequences overlap (column 7, lines 47-55), part of 32, which is the first nucleotide sequence of the second region, also hybridizes to the target. The remaining part of 32, which is in the second region, hybridizes to part of 34, which is also part of the second region, thereby forming self-hybridized second loops 33 and 36 in the detectable ribozyme structure of Figure 13 (column 14, Example V). Lizardi et al also teaches the probes have the added advantage of allowing exponential replication of the target polynucleotide (column 14,

lines 40-41), which generates up to a billion copies of a single target molecule in a single step (column 3, lines 48-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the detector comprising a probe having one terminus immobilized and the other terminus labeled with a redox moiety as taught by Blackburn et al with the switch probe of Lizardi et al with a reasonable expectation of success. The modification would result in the probe of Lizardi et al being immobilized at end 35 as shown if Figure 12 of Lizardi et al and the redox moiety at end 32 in accordance with the immobilization and labeling taught by Blackburn et al. Upon binding, end 32 would move closer to end 35, as depicted in Figure 13, thereby making the second distance provide more efficient electron transfer to the electrode because the redox moiety is now closer to the electrode. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a detector having the added advantage of having probes that allow production of a billion copies of a potentially scarce target in a single step amplification of as explicitly taught by Lizardi et al (column 3, lines 48-50).

Regarding claim 28, the detector of claim 25 is discussed above. Blackburn et al further teach the detector comprises a detector for detecting electron transduction between the electrode and the redox moiety when the second loop is formed; namely, an AC detector (column 83, lines 55-65).

Regarding claim 28, the detector of claim 25 is discussed above. Blackburn et al further teach the detector comprises an indicator for inducing electron transduction between the electrode and the redox moiety when the second loop is formed; namely, an AC initiator (column 83, lines 55-65).

Regarding claims 30-31, the detector of claim 29 is discussed above. Blackburn et al further teach the first region is at one end of the probe and the third region is at the second end of the probe because either the 3′ or 5′ terminal nucleoside of the nucleic acid probe is attached to the electrode via a conductive oligomer (column 41, lines 17-25) and the redox moiety 135 at the other terminus (Figure 12)

Regarding claims 32-33, the detector of claim 25 is discussed above. Blackburn et al further teach the electrode comprises a metal; namely, gold (column 2, lines 60-65).

Regarding claim 34, the detector of claim 33 is discussed above. Blackburn et al further teach the redox moiety is ethidium bromide (column 49, lines 15-40).

10. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn et al (U.S. Patent No. 6,264,825 B1, issued 24 July 2001) in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994) as applied to claim 1 above, and further in view of Rothberg et al (U.S. Patent Application Publication No. US 2002/0012930 A1, published 31 January 2002).

Regarding claim 13, the detector of claim 1 is discussed above in Section 8. Neither Blackburn et al nor Lizardi et al teach loops in the target and the probe in the second configuration (i.e., during hybridization).

However, Rothberg et al teach probes hybridized to targets wherein the probe and the target have a loop during hybridization; namely, Figure 1D, wherein the hybridized probe leaves a loop in the probe and target in the form of the gapped region and a loop in the form of the single stranded portion of the rolling circle template molecule (Figure 1D). Rothberg et al teach the loop in the target has the added advantage of allowing detection of single nucleotide polymorphisms in the gap (paragraph 0091). Single nucleotide polymorphisms are indicative of genetic diseases.

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector as taught by Blackburn et al in view of Lizardi et al with the loop regions in the target and the probe as taught by Rothberg et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of allowing detection of markers of genetic disease as a result of detection of single nucleotide polymorphisms in the gap as explicitly taught by Rothberg et al (paragraph 0091).

Response to Arguments

11. Applicant's arguments are considered below.

A. As noted above in Section 1, Applicant's arguments on pages 11-14 of the Remarks regarding the teachings of Lee et al have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Blackburn et al as described below.

B. Applicant's arguments on pages 15-22 regarding the teachings of Lee et al in view of Egholm et al, Rothberg et al, Lizardi et al, and Hashimoto et al rely upon the rejections presented in the previous Office Action as obvious over the teachings of Lee et al. Because the obviousness rejections based on the teachings of Lee et al have been withdrawn, the arguments are moot.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jehanne Sitton

JEHANNE SITTON
PRIMARY EXAMINER

8/13/07

Robert T. Crow
Examiner
Art Unit 1634